# of p53

Gasol Garcia, Ana

Universitat Autònoma de Barcelona, Bellaterra

Abstract

P53, also known as the "The guardian of the genome", was first described in 1979 as the first identified tumor suppressor gene. It is a crucial protein in cells, where regulates the cell cycle and it is important because of its role in conserving stability by preventing genome mutation.

Our cells face many dangers, including chemicals, viruses and ionizing radiation. For instance, if key regulatory elements are damaged, the normal controls on cell growth may be blocked and the cell will rapidly multiply and grow into a tumor. p53 tumor suppressor is one of our defenses against this type of damage.

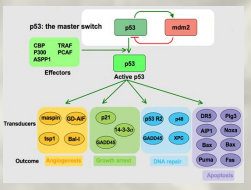
It is normally found at low levels, but when DNA damage is sensed, its levels rise and it adopts its active tetramer conformation, and initiates protective measures acting as an "emergency brake". p53 binds to many regulatory sites in the genome, acting as a transcription factor, and begins production of proteins that halt cell division until the damage is repaired. Or, if the damage is too severe, it initiates the process of apoptosis, which directs the cell to commit suicide, permanently removing the damage.

Therefore, the dissection of its apoptotic pathway it is of great importance to understand the key points of the mechanisms underlying in taking decisions and cell fate in order to design new cancer therapies.

P53 Overview

Function

Once activated, it acts as a transcriptional activator or transrepressor of genes involved in different cellular processes such as angiogenesis, growth arrest, DNA repair and apoptosis.



Choice of response

Different promotor affinities for P53

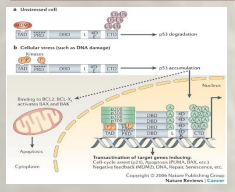
- **Growth arrest**: P21 promotor ↑ affinity , activated at low levels
- **Apoptosis**: higher levels and extensive stress

MDM2-P53 Regulation

MDM2 Inhibits p53 → P53 Shuttle from nucleus to cytoplasm for proteasome degradation

-Through its ubiquitin-ligase activity

-Quenching p53 transcription activity by occluding the p53 transactivation domain



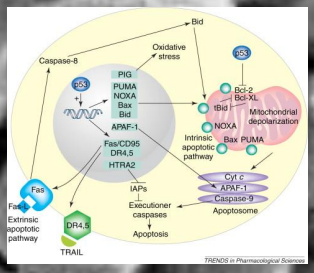
P53 Half-life: 5-20min

The apoptotic pathway

The Extrinsic pathway

Death receptors (TNF family)
- FAS
- DR5//Killer
- PERP

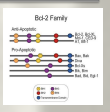
Recruit of adaptor proteins → DISC → Caspase activation



The Intrinsic pathway

Bcl2 Family

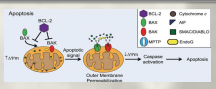
Bax and **Bak** are membrane proteins of the outer mitochondrial membrane that regulate the membrane permeabilization (MOMP). When activated, they homo-oligomerize and form the pore.



They can be activated by:

- **tBid** and **Bim**
- Directly by **p53**
- Being released from **Bcl2**, which is an anti-apoptotic protein that represses Bax and Bak. When P53 is activated, it binds to Bcl2 thereby allowing them to form the MOMP.

MOMP

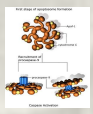


MOMP formation allows the release of caspase activation molecules such as:

- Cytochrome C
- SMAC/DIABLO
- EndoG1

Apoptosome and caspases

Apoptosoma = Apaf-1+Cytochrome C + caspase 9



Activation of effector caspases → **APOPTOSIS**

Activation

Apoptotic-related gene induction

Stress and DNA damage → Kinases (ATM,ATR..) phosphorryater P53 N-terminal → Blocking of MDM2-P53 interaction → Increase of P53 Half-life and nuclear accumulation → Tetramerization Active transcription factor

TARGET GENES: those with P53 responsive elements

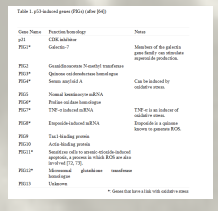
INDUCED GENES	FUNCTION
BAX	Mitochondrial pore protein
PUMA	Pro-apoptotic BH3 protein associated with Bcl2, promote Cyt C release
PERP	Pro-apoptotic transmembrane protein
NOXA	Associated with Bcl2, promote Cyt C release
Bcl2	Anti-apoptotic BH3 protein
PIGs	Apoptosis by regulation of redox potential
P53AIP	Dissipate mitochondrial potential
NF-KB	Transcription factor, mediator of TNF receptor signaling
FAS	Death receptor, procaspase 9 activation
FAS1/APO1	Death receptor ligand
DR5/KILLER	Death receptor
IGF-BP3	IGF binding protein 3, anti-mitogenic and pro-apoptotic
PIDD	"P53-induced protein with death domain", participates in death receptor signaling
APAF1	Adaptor protein for caspase 9 activation
HTRA2	Serine protease
MDM2	P53 regulator, Ubiquitin-ligase

Role of PIGs and ROS

- ROS are downstream mediators of apoptosis
- Several P53 induced genes (PIGs) are related to oxidative stress

Polyak et al. model:

1. Transcription induction of REDOX related genes
2. Formation of ROS
3. Oxidative degradation of mitochondrial components culminating in cell death



PIG3 → bioactivation of quinones → ROS production → apoptosis

Convenient apoptosis

✓**Plant meristems:** TED2 → high homology with PIG3 :↑ ROS

✓ **Cancer therapy** → control of P53, induce apoptosis in target cells

✓ **Nutlin**: small molecule that leadt to P53-MDM2 disruption

Conclusion

- P53 follows a complex regulation mechanism which enables the cell to respond accordingly with the extent of stress or damage.
- MDM2, post translational modifications and its different structural domains, is what provides P53 with its accurate sensitivity.
- The mitochondrial pore (MOMP) is under the regulation of a complex network of membrane proteins that are also transcriptionally regulated by P53.
- PIG3 and ROS are important for the apoptosis followed by oxidative stress in response to P53.
- P53 is a good candidate for cancer therapy. If we are able to control the induction of apoptosis, we could target and induce the apoptosis in cancer cells.

"Further understanding of the apoptotic pathway is without doubt a crucial step towards the development of new cancer therapies"

References

B. Vogelstein, D. Lane, and a J. Levine, "Surfing the p53 network.," *Nature*, vol. 408, no. 6810, pp. 307–10, Nov. 2000. D. P. Lane, "Cancer. p53, guardian of the genome.," *Nature*, vol. 358, no. 6381, pp. 15–6, Jul. 1992. F. Toledo and G. M. Wahl, "Regulating the p53 pathway: in vitro hypotheses, in vivo veritas.," *Nature reviews. Cancer*, vol. 6, no. 12, pp. 909–23, Dec. 2006. J. S. Fridman and S. W. Lowe, "Control of apoptosis by p53.," *Oncogene*, vol. 22, no. 56, pp. 9030–40, Dec. 2003. K. Polyak, Y. Xia, J. L. Zweier, K. W. Kinzler, and B. Vogelstein, "A model for p53-induced apoptosis.," *Nature*, vol. 389, no. 6648, pp. 300–5, Sep. 1997. L. T. Vassilev, "MDM2 inhibitors for cancer therapy.," *Trends in molecular medicine*, vol. 13, no. 1, pp. 23–31, Jan. 2007. M. Mihara, S. Erster, A. Zaika, O. Petrenko, T. Chittenden, P. Pancoska, and U. M. Moll, "P53 Has a Direct Apoptogenic Role At the Mitochondria.," *Molecular cell*, vol. 11, no. 3, pp. 577–90, Mar. 2003. S. Cory and J. M. Adams, "The Bcl2 family: regulators of the cellular life-or-death switch.," *Nature reviews. Cancer*, vol. 2, no. 9, pp. 647–56, Sep. 2002. S. Haupt, M. Berger, Z. Goldberg, and Y. Haupt, "Apoptosis - the p53 network.," *Journal of cell science*, vol. 116, no. Pt 20, pp. 4077–85, Oct. 2003. T. Soussi, E. Hickman, "The role of p53 and pRB in apoptosis and cancer," *Current Opinion in Genetics & Development*, vol. 12, no. 1, pp. 60–66, Feb. 2002. Websites: Protein data bank, p53.free.fr

Contact: ana.g.gasol@gmail.com